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A flexible approach to modeling variable absorption in the context of repeated dosing: illustrated with rifampicin

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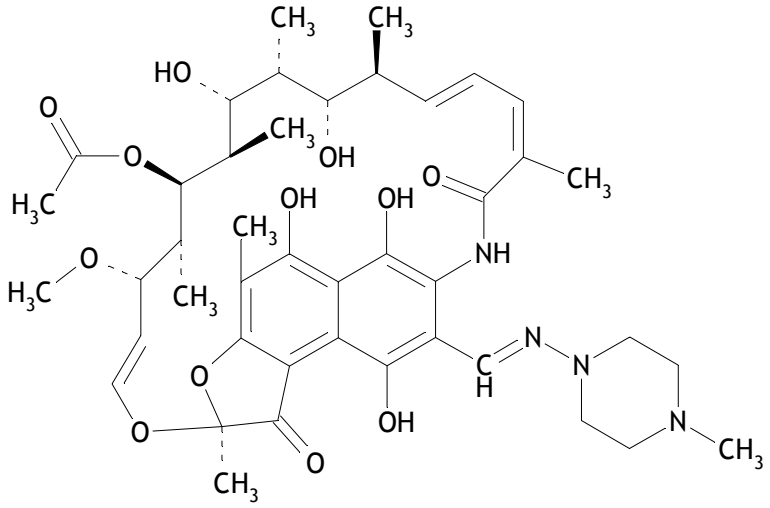
Rifampicin



- Rifampicin (rifampin, RIF) is a **key element** of combination tuberculosis chemotherapy
- Administered as first-line treatment in combination with **isoniazid** and **pyrazinamide** in both intensive and continuation phases of treatment (6-8 months)

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Data

- **Pooled** dataset
  - 3 PK studies
  - 2 913 concentration-time observations
  - Multiple dosing (450 – 600 mg) and sampling occasions
  - *n*=261 South African pulmonary tuberculosis patients
- **Combination**:
  - Rich data, fixed sampling times
  - Sparse data, within sampling time windows
- **Noisy**

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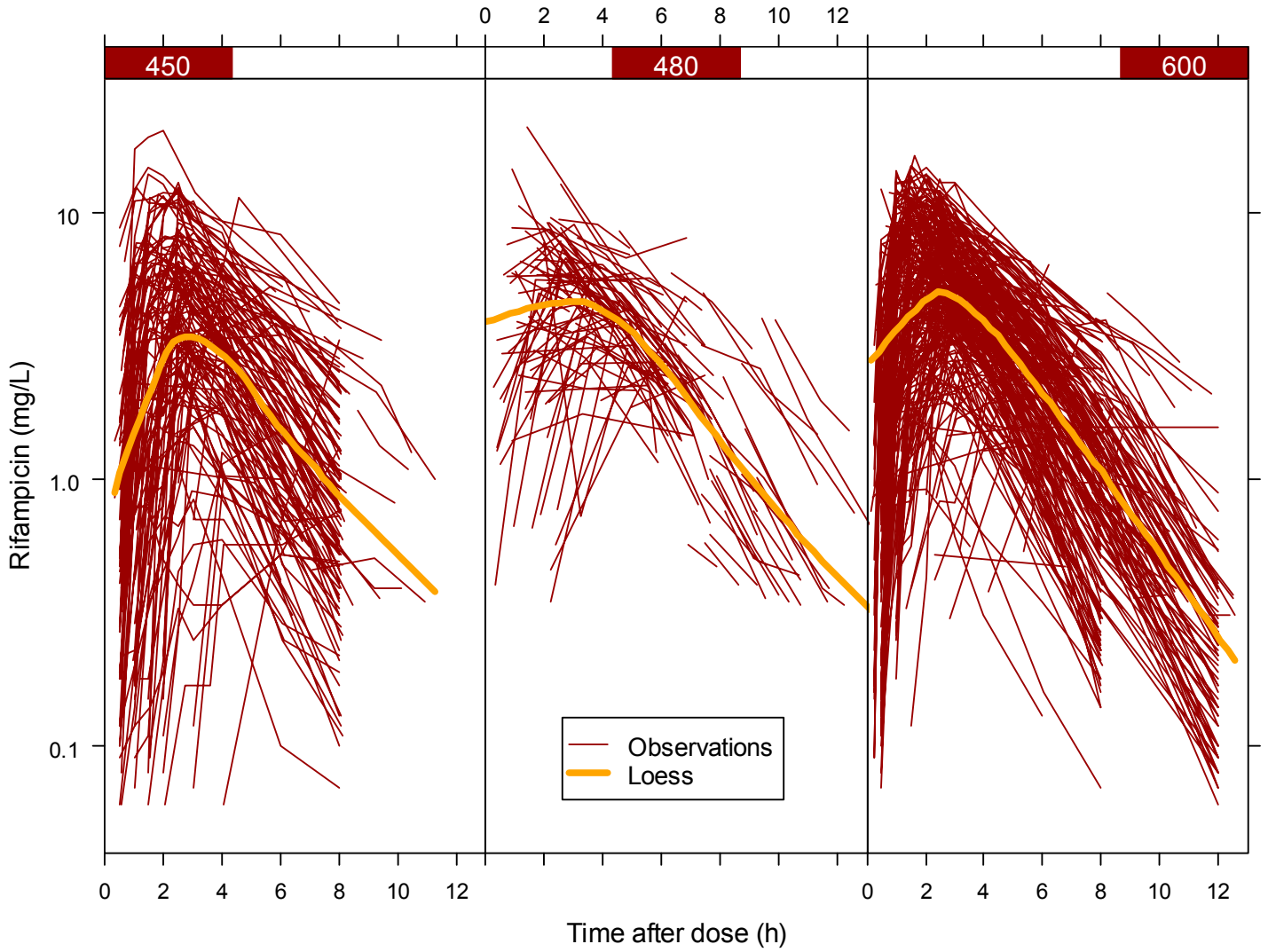
Data



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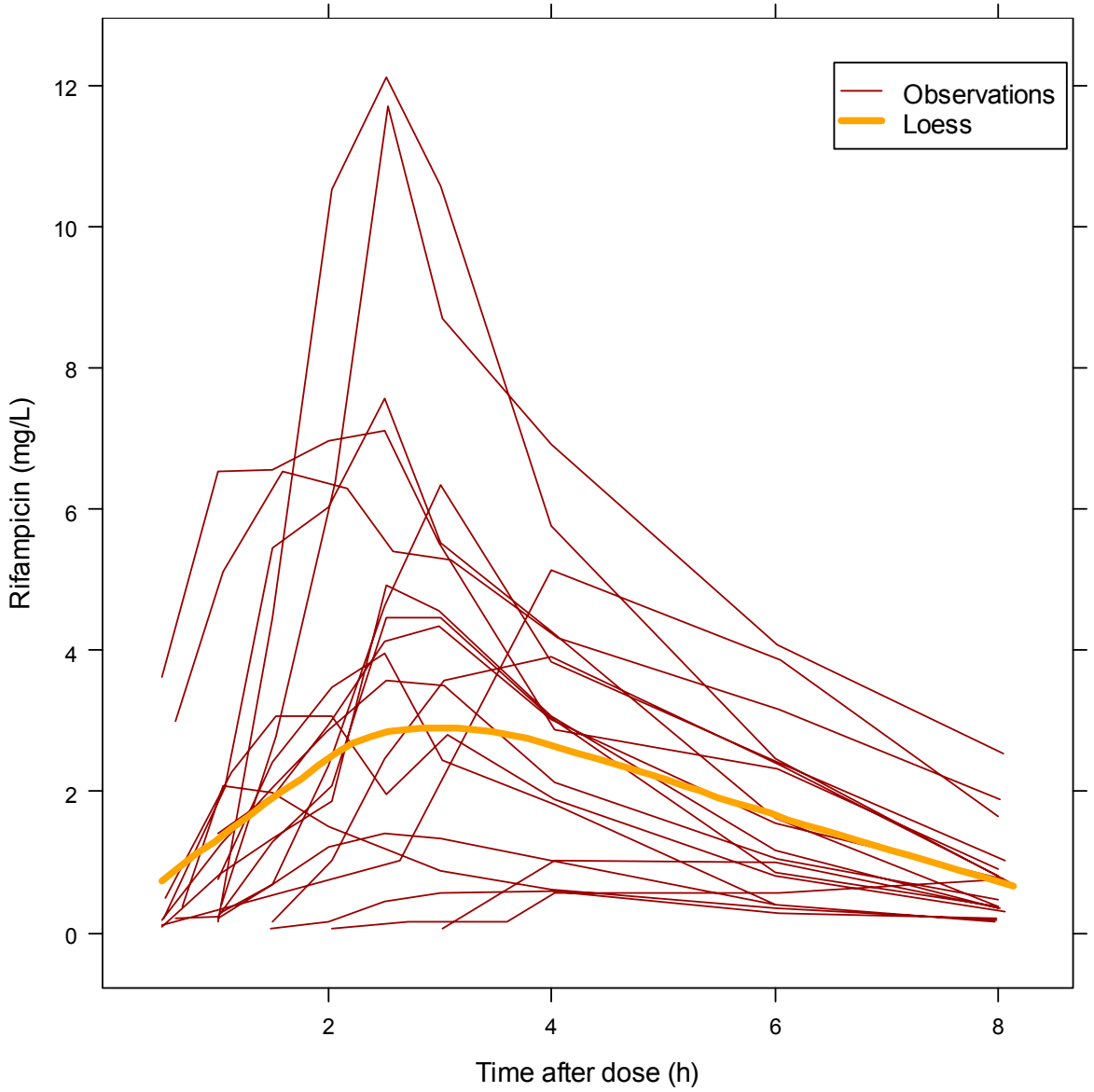
Data



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The issue…

- Comparatively large numbers of individuals in the dataset apparently experiencing **delayed or incomplete absorption**
- **Not explained** by available covariates
- Mouth checks carried out after drug administration in all cases
- No concomitant food
- Severely ill patients in some cases

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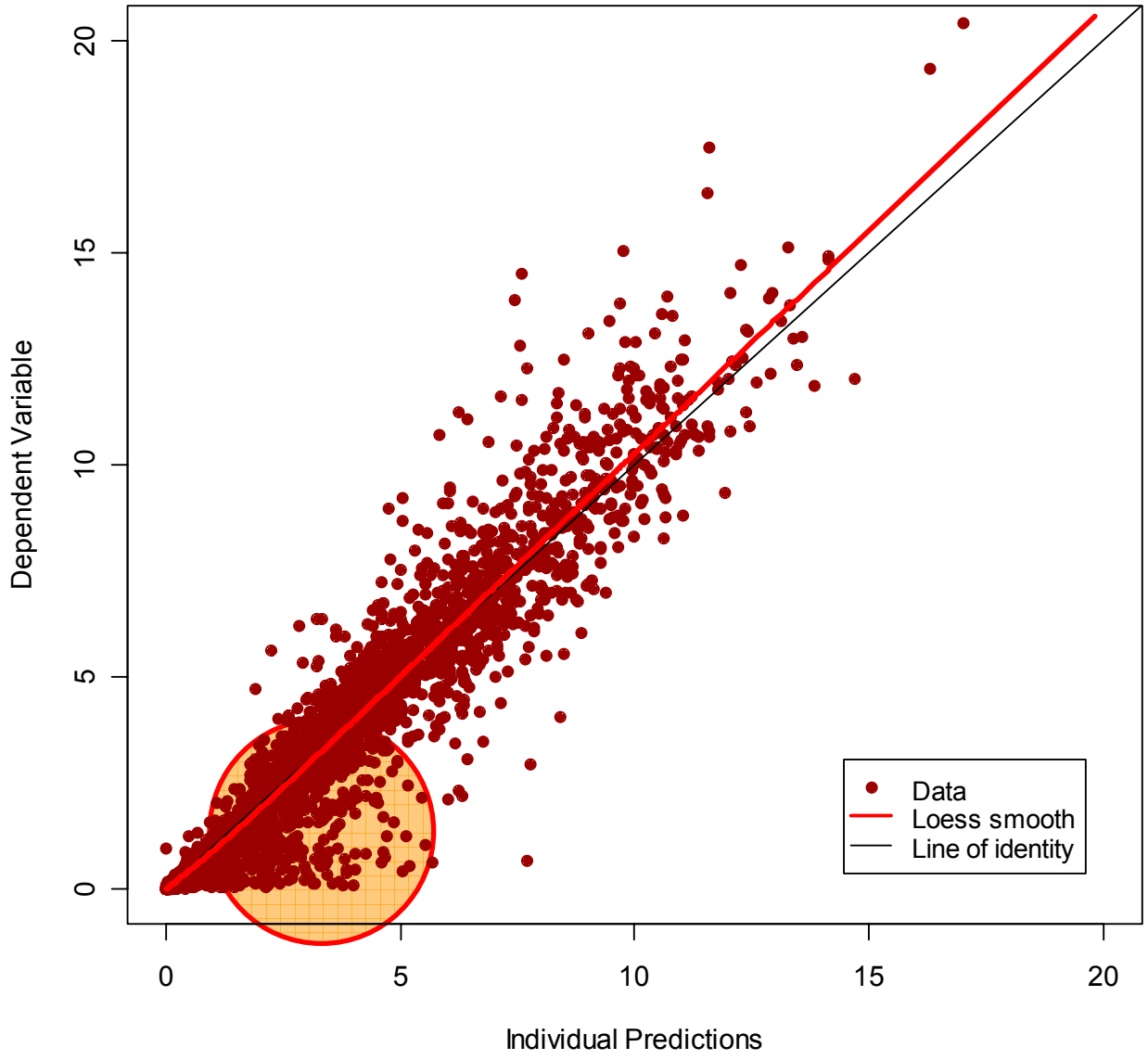
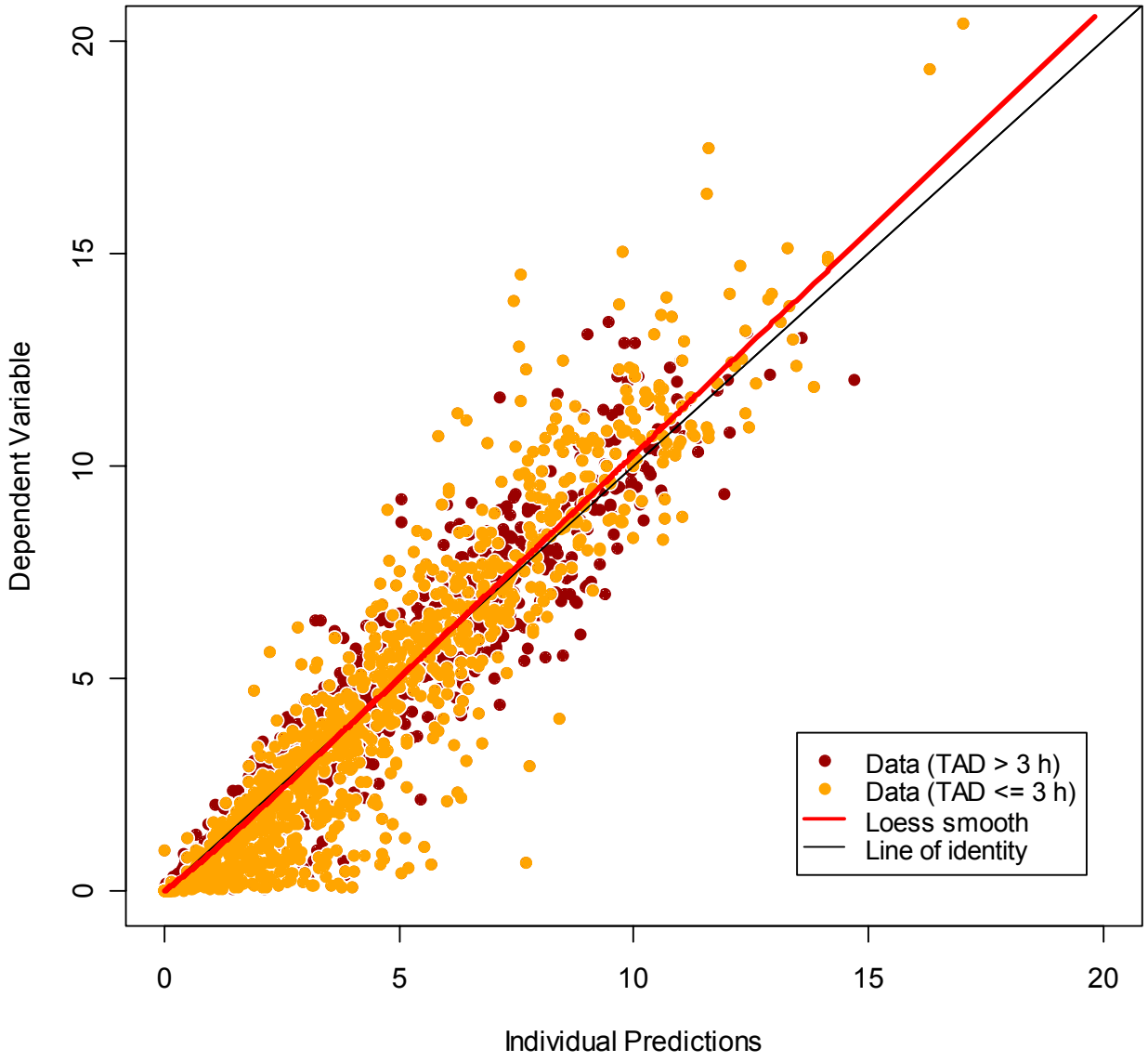
Best model fit prior to transit model…



Best model fit prior to transit model…



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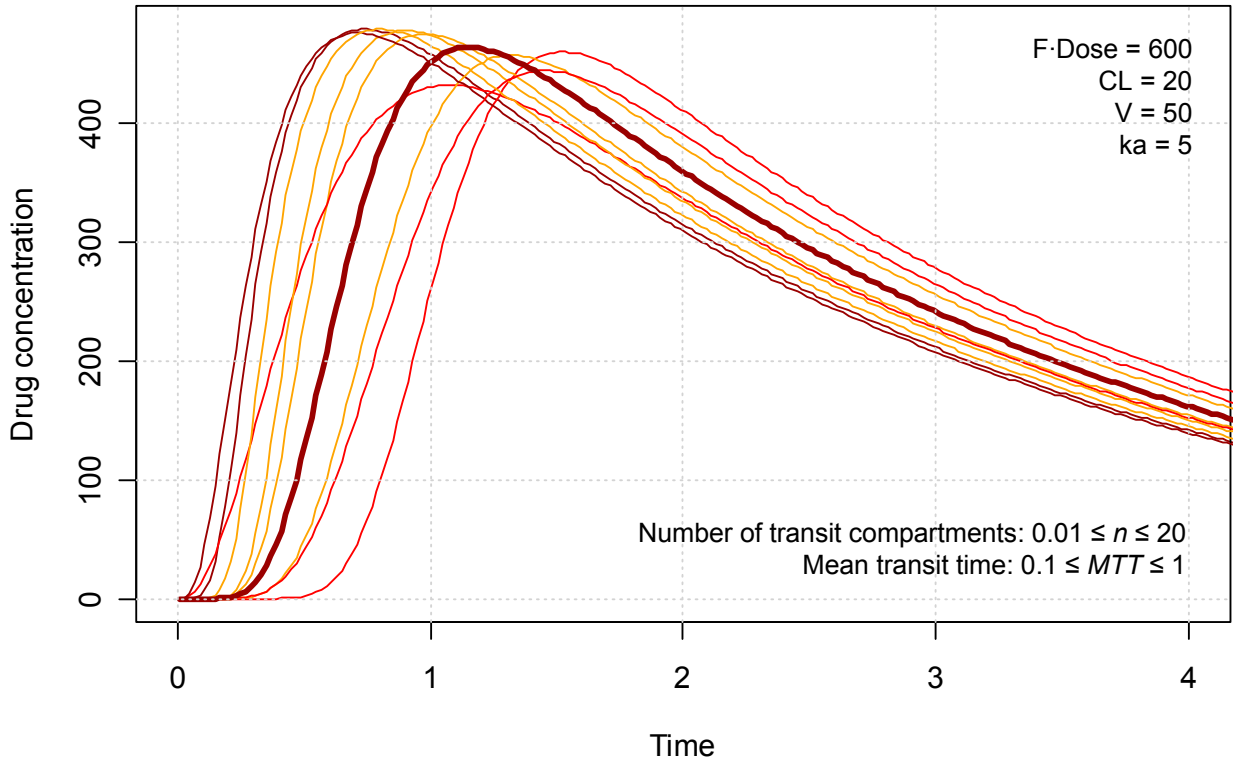
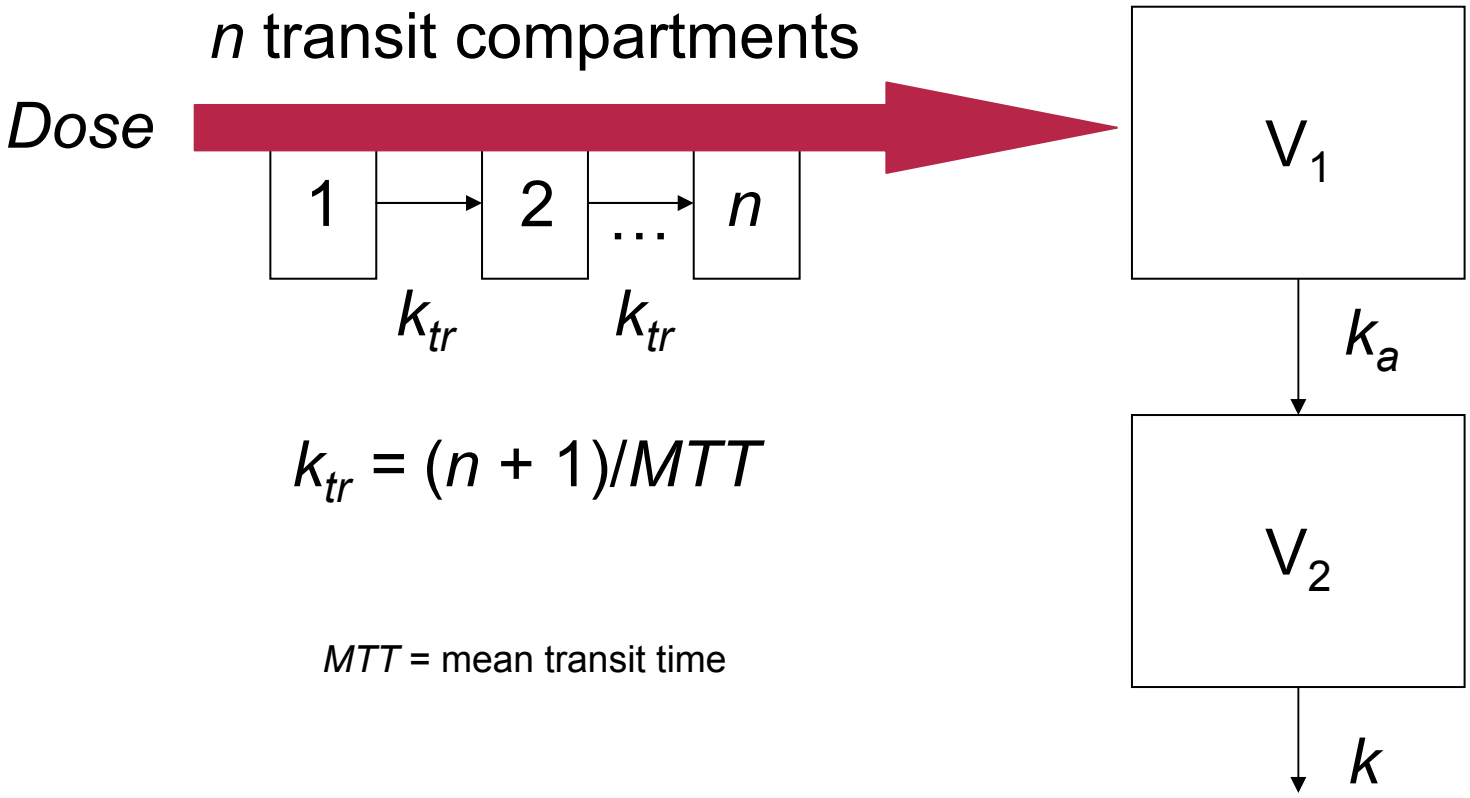
So what about the transit model (TCAM)?



Savic R, Jonker DM, Kerbusch T, Karlsson MO. **Evaluation of a transit compartment model versus a lag time model for describing drug absorption delay**. PAGE 13 (2004) Abstr 513 [www.page-meeting.org/?abstract=513]

The Transit Compartment Absorption Model



$$k_{tr} = (n + 1)/MTT$$

MTT = mean transit time

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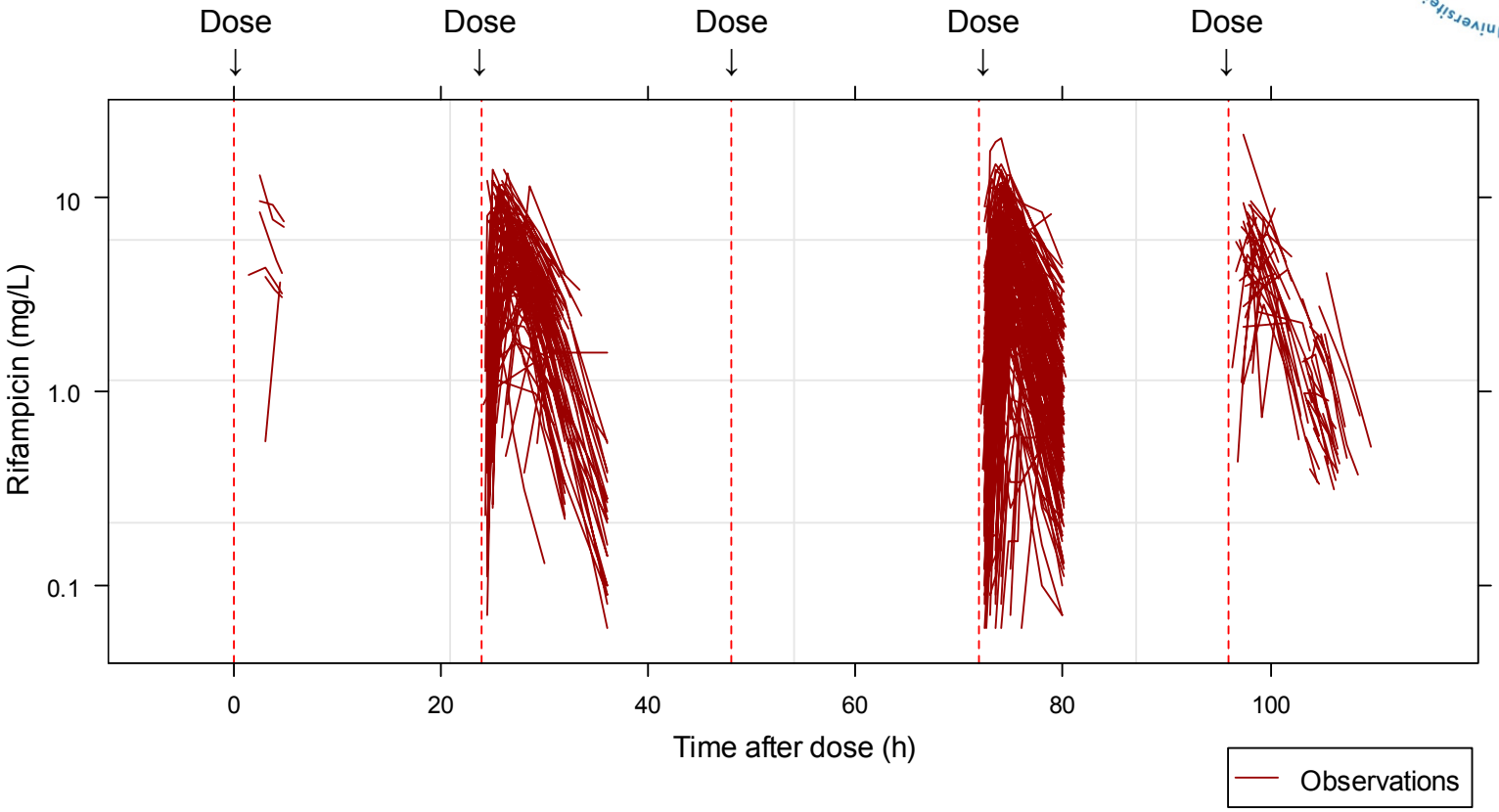
All very good, but…



- We have **repeated dosing**

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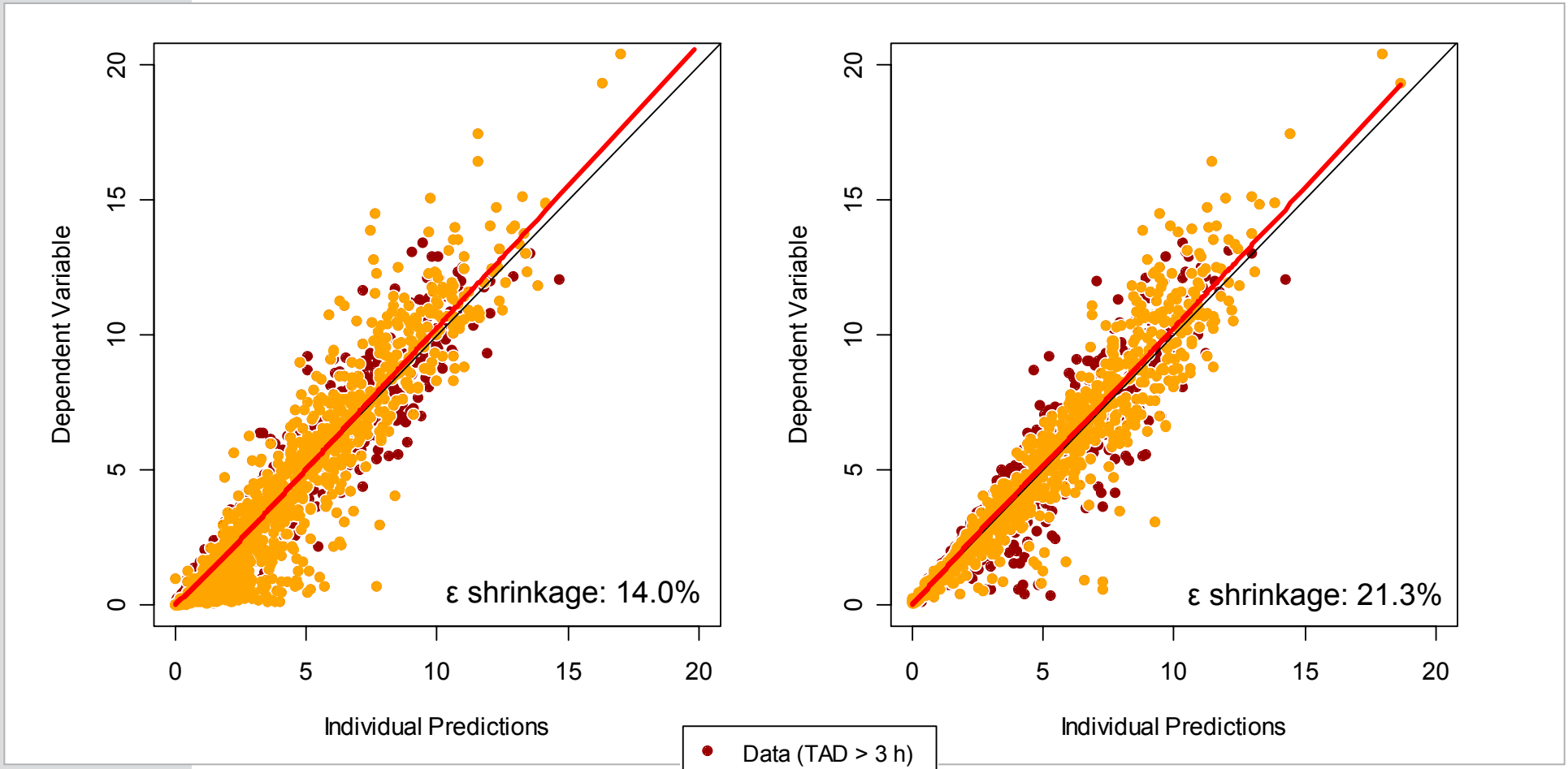
Repeated dosing

- So how to deal with repeated dosing?

$$\frac{dA_1}{dt} = F \cdot Dose \cdot \frac{\left(k_{tr} \cdot \mathbf{t_{ad}}\right)^n \cdot e^{-k_{tr} \cdot \mathbf{t_{ad}}}}{n!} \cdot k_{tr} - k_a \cdot A_1$$

- We need to include **time after dose** at each iteration – this has to be calculated on-the-fly from dosing records
- **Assume that 100% of the bioavailable dose has reached the absorption compartment** during the dosage interval

Goodness-of-fit



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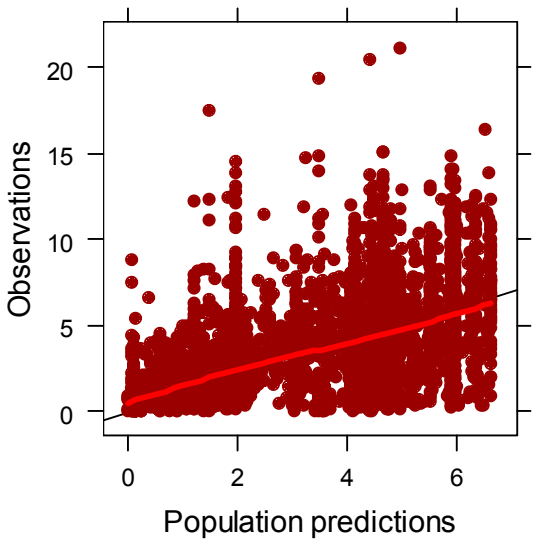
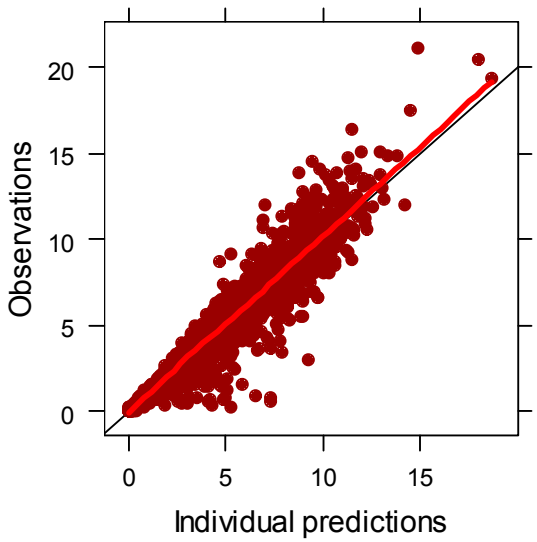
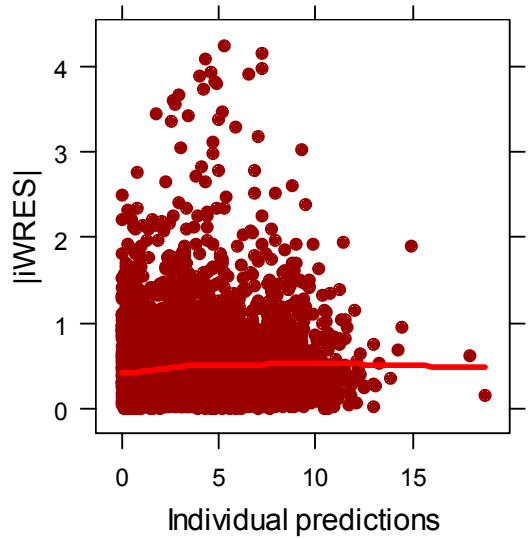
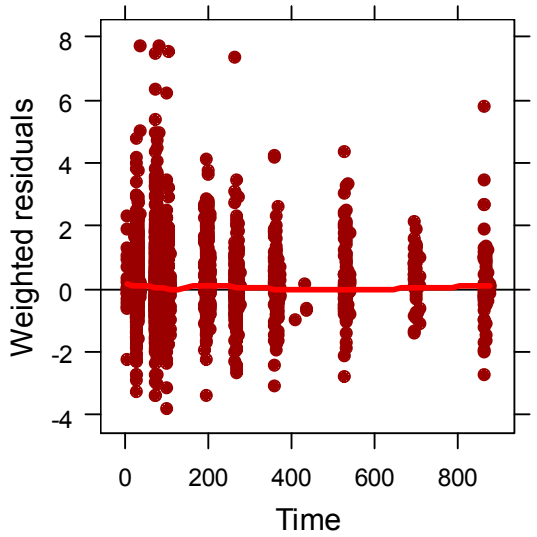
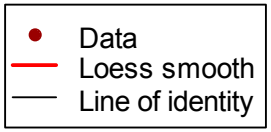
Goodness-of-fit: TCAM











Results: Parameter estimates

Absorption Model	ΔOFV (df)	*CL/F* (IIV)	*V/F* (IIV)	k_a (IIV)	ε_{ADD}	ε_{EXP}
None	0 (0)	19.4 (0.321)	52.8 (0.427)	1.61 (2.39)	0.256	0.302
Lag time	83.026 (2)	20.2 (0.387)	53.4 (0.415)	1.64 (0.689)	0.409	0.255
Sequential zero- and first-order	270.703 (2)	19.2 (0.314)	51.5 (0.384)	1.23 (0.787)	0.254	0.259
TCAM	391.939 (3)	19.2 (0.279)	53.2 (0.188)	1.15 (0.439)	0.0923	0.222

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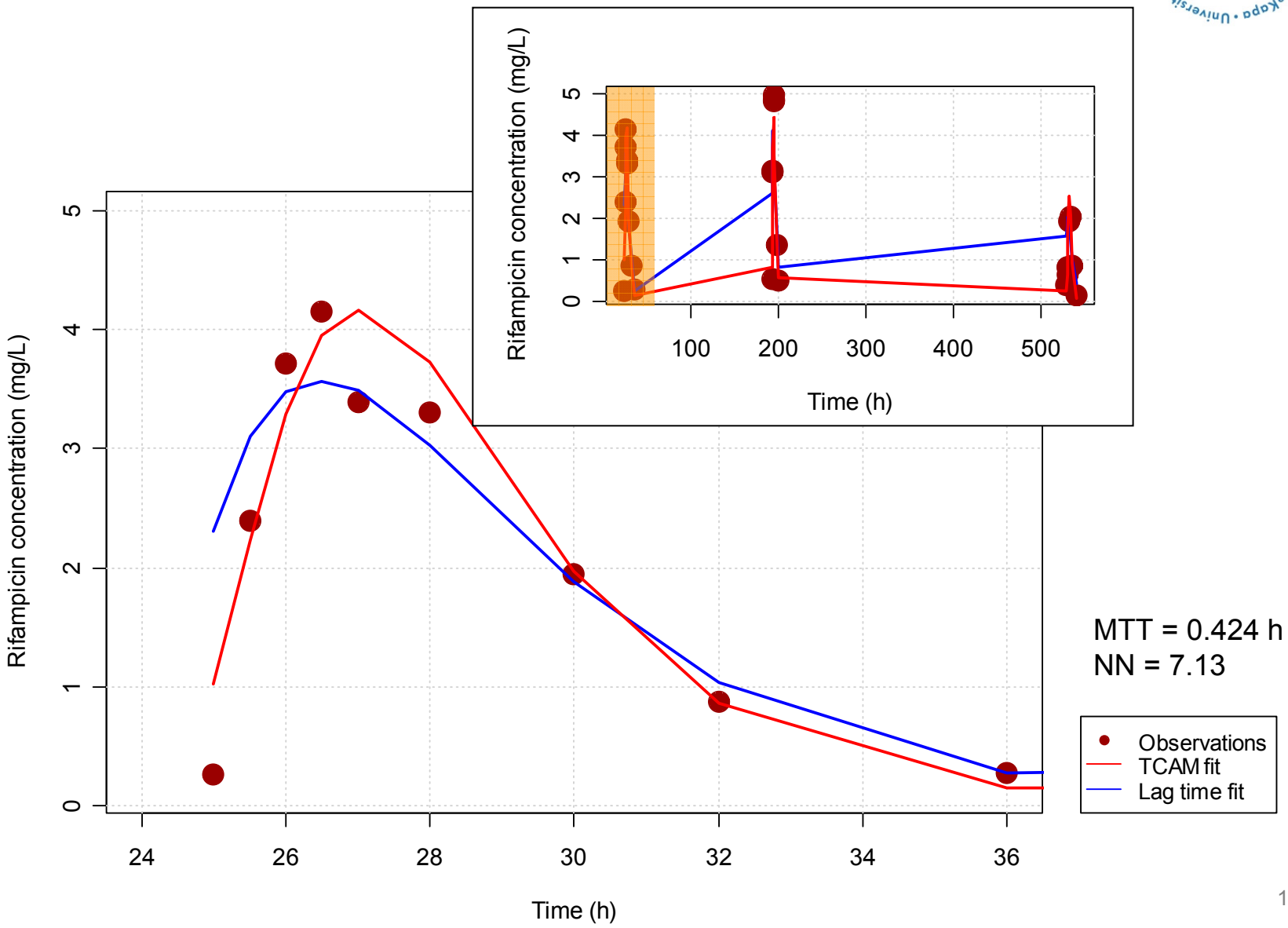
Results: Example



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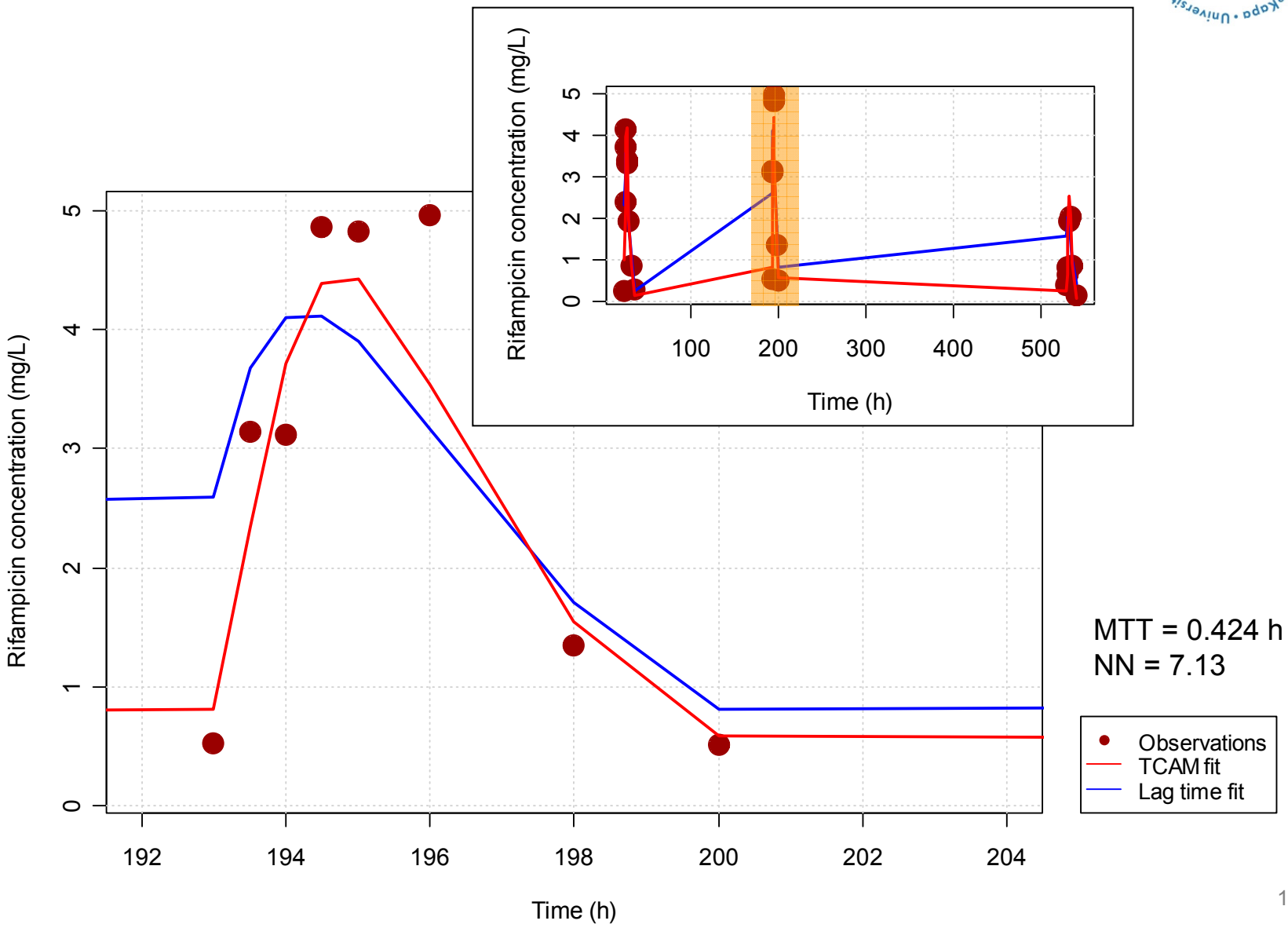
Results: Example



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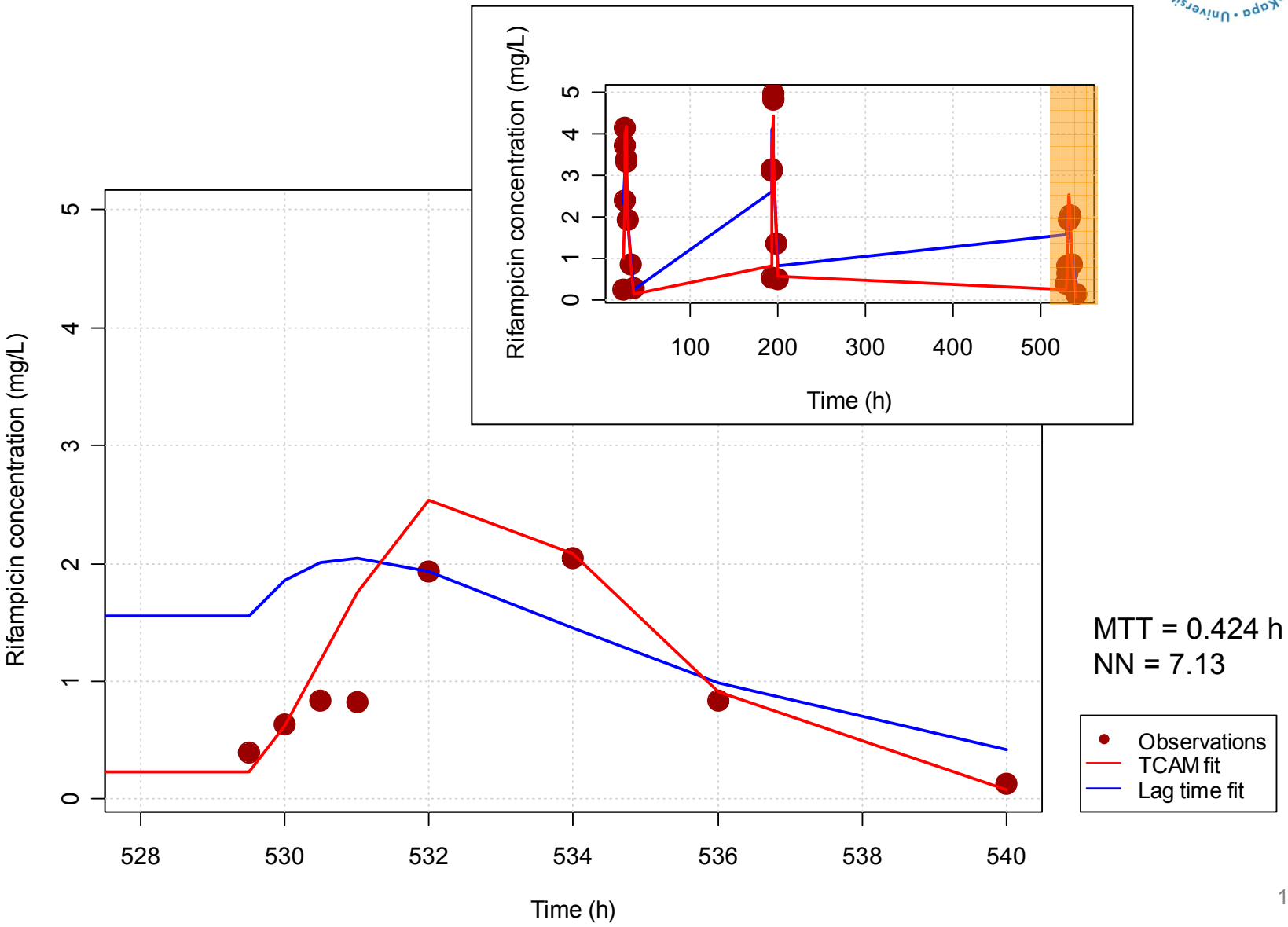
Results: Example



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In practice

- Implementation in NONMEM (**ADVAN6**)
- **$PK**
  1. **Verbatim code**: More ODE evaluations required
  2. Set **F1 = 0**
  3. Set T_{DOSE} **= TIME** if AMT > 0
  4. **MTT** and **N** added (2-4 new parameters depending on IIV structure)
  5. **KTR** is calculated
  6. **Adjustment factor** to ease ODE calculations

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In practice

- **$DES**
  - Input function is **log transformed** – ensure no log(0) by including a correction factor
  - DADT(1) is a **conditional** statement
    - If **TIME > T_{DOSE}** then use **T-T_{DOSE}** as the amount of drug entering the system
    - If **TIME = T_{DOSE}** then use **T** alone
  - Example code is available on request
- There are other ways to implement
  - **Without ODEs** in NONMEM VI

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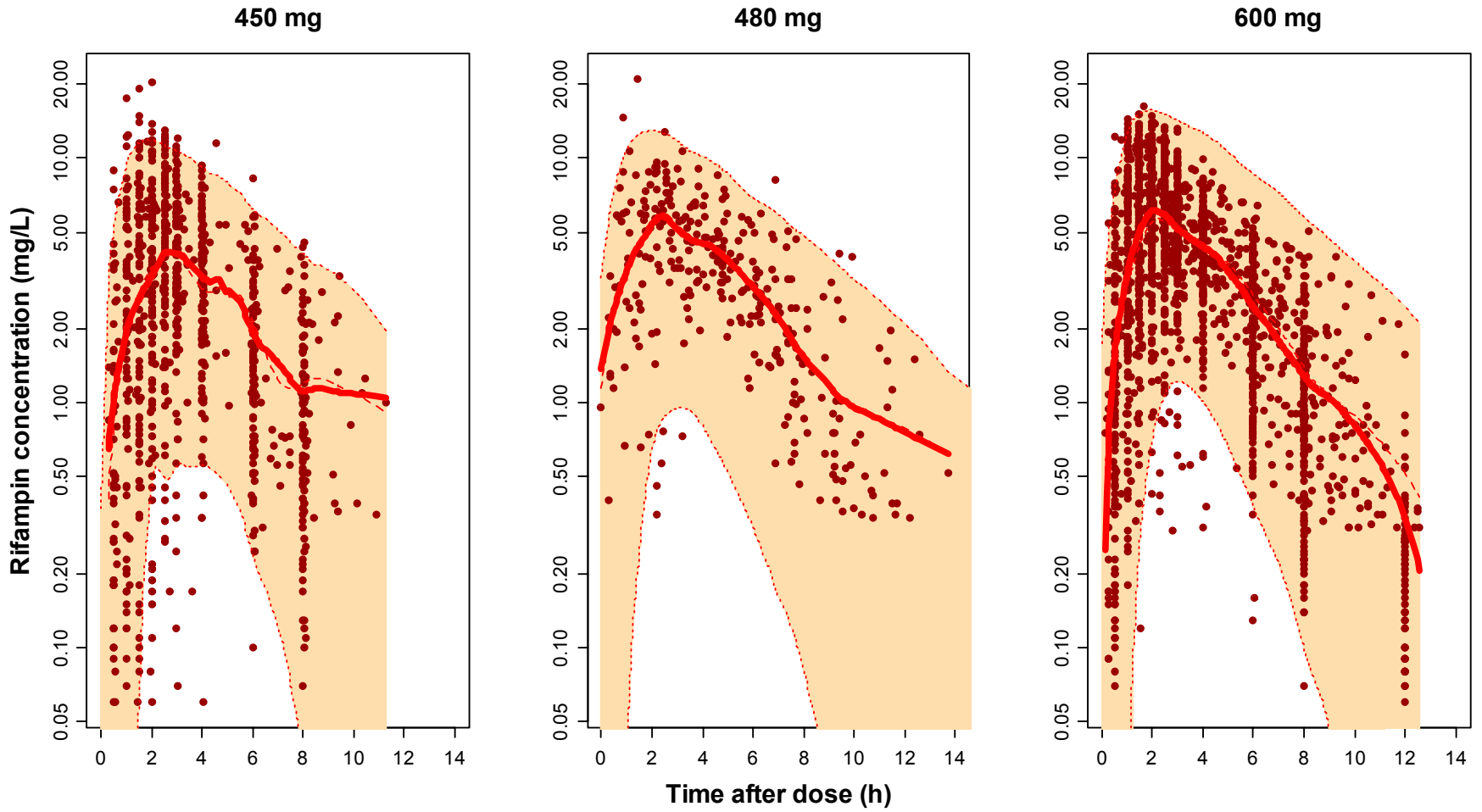
Visual predictive check



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Discussion

- Model assumes **gradual increase** in absorption rate, resulting in smoother rise towards maximum during absorption phase
- Extremely **flexible**
- (Slightly) better **physiological** approximation to the process than lag times
- Not prone to **numerical problems**
- Significant **shrinkage**…

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Conclusion

- The TCAM was easy to implement and offered **superior** fit in comparison with other methods when adapted to **multiple-dose data** in this population
- **Caveat**
  - Assumes **all of the dose** has reached the absorption compartment **before** the next is administered
  - There is a way to solve this under development (Contact Radojka Savić for details – **rada.savic@farmbio.uu.se**)

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Questions?

Grateful acknowledgments to Alicia Evans, Afia Fredericks, Mick Looby, Rudy Onia and Jean van Dyk.

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Backup slides

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Repeated dosing

- Daily dosing over a 27-day period
- The TCAM as originally implemented can only deal with single-dose data
- **Initial conditions (dose)** must be set at time 0 to support the differential equations used

$$\frac{dA_1}{dt} = F \cdot Dose \cdot \frac{\left(k_{tr} \cdot t\right)^n \cdot e^{-k_{tr} \cdot t}}{n!} \cdot k_{tr} - k_a \cdot A_1$$

k_{tr}	Rate constant for drug passage through the transit compartments
t	Time
n	Number of transit compartments
k_a	Rate constant for absorption
A_1	Amount of drug in the absorption compartment

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Example code

- Implemented using **ADVAN6**
- In **$PK**:

```
; Verbatim code to allow more ODE evaluations
"FIRST
"       COMMON/PRCOMG/  IDUM1,IDUM2,IMAX,IDUM4,IDUM5
"INTEGER IDUM1,IDUM2,IMAX,IDUM4,IDUM5
"IMAX=10000000

; Set bioavailability of the dose to 0
F1    = 0

; Set up dosing times
IF(AMT.GT.0)TDOS = TIME       ; If AMT > 0, set TDOS to TIME
TAD = TIME - TDOS             ; Set time after dose
```

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Example code

- In **$PK**:

```
; Mean transit time (MTT)
TVMTT = THETA(.)
MTT   = TVMTT*EXP(ETA(.))

; Number of transit compartments (NN)
TVNN  = THETA(.)
NN    = TVNN*EXP(ETA(.))

; Transit rate constant
KTR   = (NN+1)/MTT

; Adjustment for easing calculations
L     = LOG(2.5066)+(NN+.5)*LOG(NN)-NN+LOG(1+1/(12*NN))
```

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Example code

- In **$DES:**

```
X = 0.00001          ; To avoid log(0)

; All DADT(.) statements on a single line
; Absorption compartment
; Dose not given at this observation time
IF(T.GE.TDOS)THEN  ; if current time greater than TDOS
  DADT(1) = EXP(LOG(PD + X) + LOG(KTR + X)
    + NN*LOG(KTR*(T-TDOS) + X) - KTR*(T - TDOS) - L)
    - KA*A(1)
ELSE
; Dose given
  DADT(1) = EXP(LOG(PD + X) + LOG(KTR + X)
    + NN*LOG(KTR*T + X) - KTR*T - L)
    - KA*A(1)
ENDIF
; Central compartment
DADT(2) = KA*A(1) - K*A(2)
```